Sleep-Inducing Pharmaceuticals: A Comparison of Melatonin, Zaleplon, Zopiclone, and Temazepam

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Introduction: Current military operations often require pharmaceutical methods to sustain alertness and facilitate sleep in order to maintain operational readiness. This study was designed to compare the sleep-inducing power of four medications. ***Method:*** There were 9 men and 14 women, ages 21–53 yr, who were assessed for psychomotor performance before and for 7 h after ingestion of a single dose of placebo, zaleplon 10 mg, zopiclone 7.5 mg, temazepam 15 mg, or time-released melatonin 6 mg. The experimental design was a double-blind crossover with counterbalanced treatment order. Subjects wore polysomnographic electrodes to record total sleep and sleep latency during 4-min periods with eyes closed immediately before and after each psychomotor test sequence. Subjective drowsiness was assessed by questionnaire. ***Results:*** There were drug × trials interactions for zaleplon, zopiclone, and temazepam for total sleep, sleep latency, and subjective drowsiness. More sleep, shorter sleep latency, and more drowsiness occurred immediately after psychomotor testing compared to before testing for all medications. Melatonin did not cause any sleep prior to psychomotor testing sessions, but caused sleep and reduced sleep latency after psychomotor test sessions from 1¼ h to 4¼ h post-ingestion. ***Conclusions:*** The sleep-inducing power of the medications before psychomotor testing was zopiclone > zaleplon > melatonin > temazepam. The corresponding effect after psychomotor testing was zopiclone > melatonin > zaleplon > temazepam.

Keywords: zaleplon, zopiclone, temazepam, melatonin, sleep induction, military operations.

THE SCIENCE OF chronobiology is yielding advances in fatigue management by use of pharmaceuticals to facilitate sleep (7,8) and to sustain alertness (11). To date much of this research has been in support of military aircrew, but there is interest in such approaches to fatigue management in support of Army and Naval forces. Our laboratory recently completed an operational evaluation demonstrating the efficacy of melatonin and zopiclone as facilitators of early circadian aircrew sleep during air transport operations to sustain our troops in Bosnia (10).

Zaleplon (Starnoc®) is a newer benzodiazepine derivative with a short half-life of only 1 h (6). In contrast to zaleplon (Starnoc®), zopiclone (Imovane®) has a 5-h half-life (4) and temazepam (Restoril®) has a half-life which is a function of its formulation. The European soft gelatin capsule formulation has a 5- to 7-h half-life (5,6), whereas the North American hard gelatin temazepam formulation used in this study has a reported half-life ranging from 3.5 to 20 h (mean 9 h) (2). We recently completed a placebo-controlled single-dose study (9) to evaluate zaleplon (Starnoc®) against the 2 hypnotics zopiclone and temazepam and the hormone melatonin for impact on psychomotor performance. The results of that study indicated that the time-released formulation of melatonin (Circadin®) had no effect on performance, with increasing effects on performance noted with zaleplon, temazepam, and zopiclone, respectively. The medication effects on sleep latency and sleep, as well as subjective sleepiness, were assessed in that study during 4-min breaks immediately before and immediately after each psychomotor test session. Whereas the first paper (9) from this work was to compare these pharmaceuticals for post-ingestion depth and duration of impact on psychomotor performance, the current paper is concerned with comparing these same pharmaceuticals for their respective sleep-inducing power.

METHODS

A randomized, double-blind repeated-measures protocol was designed to assess the impact of zaleplon, zopiclone, temazepam, and time-released melatonin (Circadin®) on psychomotor performance; compare the sleep-inducing power of each medication; and monitor subjective levels of drowsiness for each medication. The protocol was approved by the DRDC-Toronto Human Research Ethics Committee. The subjects were 23 volunteers ranging in age from 21 to 53 yr (mean: 29.9 ± 10.3 yr). All subjects provided written informed consent in accordance with the declaration of Helsinki. All participants first passed a screening medical that eliminated any subjects for whom these medications were contra-indicated or who were taking prescription or over-the-counter medications. Because any of these medications (zaleplon, zopiclone, temazepam, or mela-

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tonin) could be potentially harmful to a fetus, any female who wished to participate was first required to undergo medical screening to preclude pregnancy. In order to avoid confounding study results, subjects were instructed to abstain from the use of hypnotics or psychoactive drugs (tranquilizers) for 2 wk before any experimental session, and from alcohol or over-the-counter medications within 12 h of each experimental session. The subjects were instructed to maintain regular sleep/wake cycles during the study and, to confirm normal sleep patterns, were asked to fill in a daily sleep questionnaire on awakening for 3 d prior to each experimental session. Subjects were compensated for their participation according to the DRDC-Toronto guidelines for subject stress allowance.

Subjects were run on their assigned weekly test day (one condition per test day per week) over a 5-wk period for each condition (placebo, zaleplon, zopiclone, temazepam, melatonin). Standard clinical doses of zaleplon 10 mg, zopiclone 7.5 mg, and temazepam 15 mg were used, as well as time-released melatonin 6 mg (Circadin®, Neurim Pharmaceuticals, Tel Aviv, Israel), which we used in an earlier work (8). Prior to the study, regulatory approval for the use of melatonin was obtained from the Therapeutic Products Directorate of Health Canada. In order to maintain the double-blind nature of this work, all medications (placebo, zaleplon, zopiclone, temazepam, and melatonin) were prepared in identical capsule format by a contract pharmacy (Central Medical Pharmacy, Toronto, Canada). All medications were administered by the principal investigator or his designate in accordance with the dosing protocol established by the contract pharmacy.

The order of medication conditions was randomized across subjects by the contract pharmacy. On the test days, each subject performed a baseline psychomotor test session before ingestion of a single dose of medication at 09:45. Thereafter the subjects were tested for psychomotor performance once every hour, beginning at 10:00 for 7 h, commencing at the 'top of the hour.' Due to the significant expense for drug blood assays, serial blood samples were drawn from only 10 subjects. Blood was withdrawn (via a catheter in the cubital vein) at hourly intervals post-ingestion for each medication in order to compare any performance changes with changes in the blood levels of each drug (or its metabolites).

EEG

The subjects were monitored for EEG evidence of sleep in order to compare the soporific/hypnotic power of the study medications. The four EEG electrodes were C3, C4, a mastoid reference, and a forehead ground. In order to obtain optimum temporal resolution of drug effects on sleep and drowsiness, the subjects performed a 4-min 'eyes-closed' session twice per hour, essentially immediately prior to and immediately after each psychomotor test session. Computer-generated instructions directed the subjects to activate an event marker on their EEG recording apparatus and to close their eyes, resting their hands on their lap or their desk, for 4 min. At the end of the 4 min, the subjects were each tapped on the shoulder and completed a computer-generated 7-point Likert scale for subjective drowsiness. These 7 points in increasing order of drowsiness were: awake and relaxed; alert and somewhat relaxed; very relaxed and a bit drowsy; very drowsy and almost fell asleep; extremely drowsy and may have fallen asleep; fell asleep a number of times; and fell asleep and stayed asleep until tapped. These categories were assigned the numbers 1–7, respectively, and the participants chose a number. Using the Rechtschaffen and Kales technique, the EEG records were analyzed to determine whether or not subjects fell asleep during these 4-min eyes-closed epochs and if so, to determine their sleep latency and total time spent asleep in each of these 4-min sessions.

Statistical Analysis

The dependent variables from the EEG files and from the questionnaires are plotted over time (independent variable) in order to establish the manner in which EEG and drowsiness changed over time (eight trials) for each of the drug conditions. All dependent variables (from all data sets) were submitted to repeated-measures analysis of variance. A priori, for each parameter, we decided to test each drug against placebo. The Least Significance Difference test was used for post hoc assessment of any main effects or interactions. The significance level was set at 0.05 for the ANOVAs and for post hoc testing of the significant drug × trial interactions.

RESULTS

EEG Data–Sleep Latency and Sleep

The total sleep data is illustrated in **Fig. 1**. By looking at Fig. 1, it is evident that the post-psychomotor test total sleep time is quite different from the pre-psychomotor test values. In order to assess this pre/post difference, the ANOVA included a pre/post factor. This 3-factor repeated-measures ANOVA had 5 levels of drug × 8 levels of trial × 2 levels of pre/post. The ANOVA yielded a main effect of drugs [$F(4,88) = 3.97$, $p < 0.005$]; a main effect of trial [$F(7,154) = 10.70$, $p < 0.00001$]; a main effect of pre/post [$F(1,22) = 35.22$, $p < 0.00001$]; a drug × trial interaction [$F(28,616) = 2.27$, $p < 0.0002$], and a trial × pre/post interaction [$F(7,154) = 4.15$, $p < 0.0003$]. Post hoc testing of the main effect of pre/post revealed that there was more post-psychomotor testing total sleep ($p < 0.00001$) than pretest sleep (47.5 s of sleep post-test vs. 5.1 s pretest). Post hoc testing of the main effect of drug revealed that zopiclone caused more sleep than the other drug conditions (**Table I**, Fig. 1a and 1b).

The sleep latency data from the 4-min (240 s) eyes-closed sessions was analyzed using the same 3-way ANOVA, which revealed the following significant effects: a main effect of drug [$F(4,88) = 3.79$, $p < 0.007$]; a main effect of trial [$F(7,154) = 11.34$, $p < 0.00001$]; a main effect of pre/post [$F(1,22) = 39.5$, $p < 0.00001$]; a drug × trial interaction [$F(28,616) = 2.19$, $p < 0.0004$], and a trial × pre/post-interaction [$F(7,154) = 4.33$, $p < 0.0002$]. Post hoc testing of the main effect of pre/post

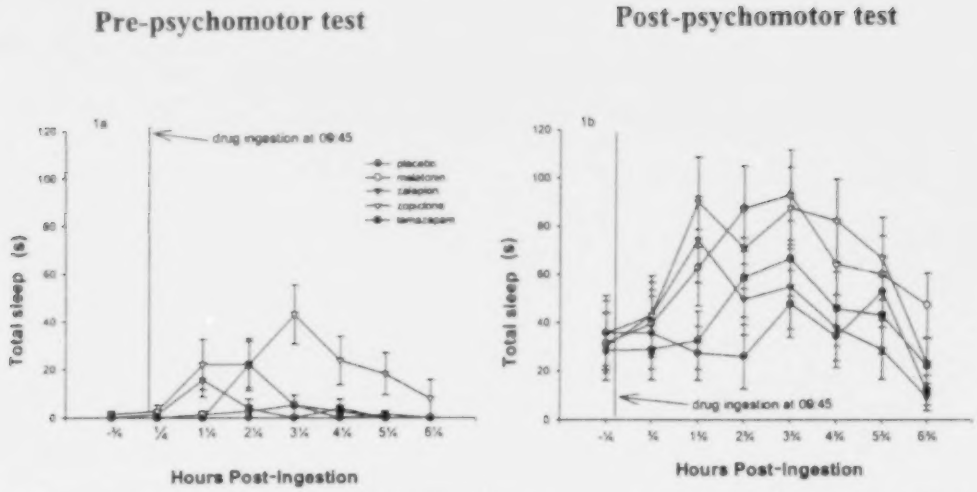

Fig. 1. Total sleep during 4-min eyes-closed rest periods both pre- and post-psychomotor testing (1a and 1b, respectively). All values are mean ± SEM and are plotted over drugs and hours post-ingestion.

revealed that the subjects had shorter sleep latencies after psychomotor testing ($p < 0.000003$) than before psychomotor testing (188.2 s post-test vs. 234.3 s pre-test). Post hoc testing of the main effect of drug (for sleep latency) indicated that zopiclone resulted in shorter sleep latencies than the other drug conditions (**Fig. 2a and 2b**). Fig. 1a illustrates that while subjects were on placebo they rarely fell asleep in the pre-psychomotor-test, 4-min eyes-closed session and if they did fall asleep it was relatively late in the 4-min sleep window (Fig. 2a). However, during the post-psychomotor test, 4-min eyes-closed sessions, they fell asleep more often (Fig. 1b) and more quickly (Fig. 2b) than they did prior to undergoing psychomotor testing (Fig. 1a and 2a).

In order to compare the effects of each drug against placebo for total sleep and sleep latency (during the 4-min eyes-closed sessions) we used a 2-factor repeated-measures ANOVA (2 drugs × 8 trials). For the pre-psychomotor test assessments of total sleep (Fig. 1a), the drug × trial interaction comparing melatonin against placebo over trials for impact on total sleep was not significant. However, the same ANOVA run on the zaleplon data confirms the drug × trial interaction was significant [$F(7,154) = 2.85$, $p < 0.008$]. Post hoc testing of this interaction confirms that while the subjects were on zaleplon, they slept more than when on placebo only at ¼ h post-ingestion ($p < 0.0004$, Table I). In contrast, post hoc testing of the drug × trial interaction for zopiclone [$F(7,154) = 3.39$, $p < 0.002$] confirms that total sleep was first different from placebo at 1¼ h post-ingestion ($p < 0.003$), with the maximum amount of zopiclone-induced sleep occurring 3¼ h post-ingestion ($p < 0.00001$), with decreasing sleep thereafter, but not

TABLE I. POST HOC RESULTS FOR PRE- AND POST-PSYCHOMOTOR TASK TOTAL SLEEP DURING THE 4-MIN EYES-CLOSED PERIODS, WHERE EACH OF THE FOUR EXPERIMENTAL DRUGS IS COMPARED TO PLACEBO OVER EIGHT TRIALS.

Pretest Total Sleep

	Time (h) relative to drug ingestion							
Drug	−¾	¼	1¼	2¼	3¼	4¼	5¼	6¼
Melatonin	ns*	ns	ns	ns	ns	ns	ns	ns
Zaleplon	ns	0.00004	ns	ns	ns	ns	ns	ns
Zopiclone	ns	ns	0.003	0.003	0.00001	0.004	0.02	ns
Temazepam	ns	ns	ns	0.00001	ns	ns	ns	ns

Post-test Total Sleep

	Time (h) relative to drug ingestion							
Drug	−¼	¼	1¼	2¼	3¼	4¼	5¼	6¼
Melatonin	ns	ns	0.009	0.00001	0.001	0.03	ns	0.01
Zaleplon	ns	0.0005	ns	ns	ns	ns	ns	ns
Zopiclone	ns	ns	0.00001	0.001	0.004	0.0006	ns	ns
Temazepam	ns	ns	ns	ns	ns	ns	ns	ns

*ns = not significant, or respective p-values.

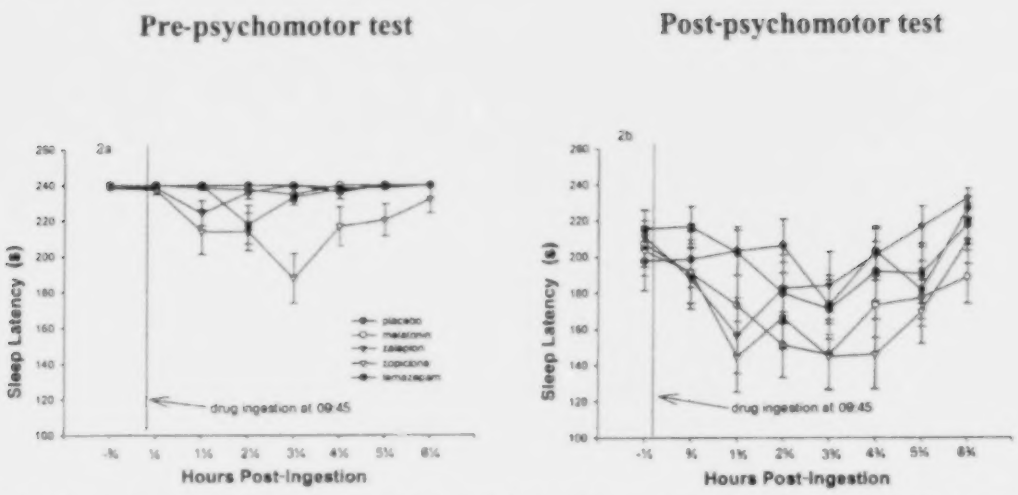

Fig. 2. Sleep latency during 4-min eyes-closed rest periods both pre- and post-psychomotor testing (2a and 2b, respectively). All values are mean ± SEM and are plotted over drugs and hours post-ingestion.

returning to placebo levels until the last psychomotor test session of the day at 6¼ h post-ingestion (Table I). The pre-psychomotor test drug × trial interaction assessing the impact of temazepam [$F(7,154) = 3.62$, $p < 0.001$] indicates that temazepam impacted on total sleep ($p < 0.00001$) only at 2¼ h post-ingestion (Table I).

Using the same protocol to evaluate the post-psychomotor total sleep data, we determined that the drug × trial interaction for melatonin vs. placebo (Fig. 1b), unlike the pre-psychomotor test total sleep data shown in Fig. 1a, was significant [$F(7,154) = 2.78$, $p < 0.009$]. Post hoc testing revealed that total sleep on melatonin was increased compared with placebo beginning 1¾ h post-ingestion ($p < 0.009$) through to the last testing session at 6¾ h ($p < 0.01$). A transient increase in sleep on placebo at 5¾ h made the difference non-significant at that single test period (Fig. 1b, Table I). The drug × trial interaction assessing the post-psychomotor test impact of zaleplon on total sleep was significant [$F(7,154) = 2.53$, $p < 0.02$]. Here post hoc testing revealed an increase in total sleep due to zaleplon, relative to placebo, that was only evident 1¾ h post-ingestion ($p < 0.0005$, Table I). The same post-psychomotor test assessment of the impact of zopiclone on total sleep indicated a significant drug × trial interaction [$F(7,154) = 2.87$, $p < 0.008$]. Post hoc testing of this interaction confirmed zopiclone-induced increases in post-psychomotor test total sleep from 1¾ h ($p < 0.00001$) to 4¾ h ($p < 0.0006$) post-ingestion (Table I). The drug × trial interaction evaluating the post-psychomotor test impact of temazepam on total sleep was not significant.

For the pre-psychomotor test assessments of sleep latency (Fig. 2a), the 2-factor ANOVA (2 drugs × 8 trials) indicated that the drug × trial interaction comparing melatonin against placebo over trials for impact on total sleep was not significant. However, the same ANOVA run on the total sleep data for zaleplon was significant [$F(7,154) = 2.77$, $p < 0.01$]. Post hoc testing revealed that zaleplon only reduced sleep latency at 1¼ h post-ingestion ($p < 0.0004$, **Table II**). The drug × trial interaction assessing the impact of zopiclone on sleep latency was significant [$F(7,154) = 3.98$, $p < 0.0005$]. Post hoc testing of this interaction revealed a zopiclone-induced shortening of sleep latency from 1¼ h post-ingestion ($p < 0.002$) to 5¼ h post-ingestion ($p < 0.03$), with the peak effect occurring 3¼ h post-ingestion ($p < 0.00001$, Table II). The corresponding drug × trial interaction assessing the effect of temazepam on sleep latency was significant [$F(7,154) = 3.64$, $p < 0.001$] with post hoc testing revealing a temazepam-induced sleep latency reduction only at 2¼ h post-ingestion ($p < 0.0001$, Table II).

The drug × trial interaction assessing the post-psychomotor test effects of melatonin on sleep latency (Fig. 2b) was significant [$F(7,154) = 2.13$, $p < 0.04$]. Post hoc testing of this interaction revealed that melatonin first significantly reduced post-psychomotor test sleep latency at 1¾ h ($p < 0.04$), with the effect peaking 3¾ h post-ingestion. Except for a loss of significance at 5¾ h post-ingestion (due to a transient decrease in sleep latency while the subjects were on placebo), the effect of melatonin on sleep latency was still evident 6¾ h post-ingestion ($p < 0.008$, Table II). The post-psychomotor test impact of zaleplon on total sleep was significant [$F(7,154) = 2.64$, $p < 0.01$]. Post hoc testing indicated that the effect of zaleplon on post-psychomotor test sleep latency was manifested 1¾ h ($p < 0.003$) and 5¾ h post-ingestion ($p < 0.02$, Table II). However, the sleep latency difference between placebo and zaleplon at 5¾ h post-ingestion was due to the fact that sleep latency was shorter while the subjects were on placebo than when they were on zaleplon. Arguably, zaleplon only reduced post-psychomotor test sleep latency 1¾ h post-ingestion. The drug × trial interaction assessing the effects of zopiclone on post-psychomotor test sleep latency was significant [$F(7,154) = 2.49$, $p < 0.02$]. Post hoc testing of this interaction indicates that zopiclone reduced post-psychomotor test sleep latency between 1¾ h ($p < 0.0001$) and 4¾ h ($p < 0.0002$) post-ingestion

TABLE II. POST HOC RESULTS FOR PRE- AND POST-PSYCHOMOTOR TASK SLEEP LATENCY DURING THE 4-MIN EYES-CLOSED PERIODS, WHERE EACH OF THE FOUR EXPERIMENTAL DRUGS IS COMPARED TO PLACEBO OVER EIGHT TRIALS.

Pretest Sleep Latency

	Time (h) relative to drug ingestion							
Drug	-¼	¼	1¼	2¼	3¼	4¼	5¼	6¼
Melatonin	ns	ns	ns	ns	ns	ns	ns	ns
Zaleplon	ns	ns	0.0004	ns	ns	ns	ns	ns
Zopiclone	ns	ns	0.002	0.002	0.00001	0.009	0.03	ns
Temazepam	ns	ns	ns	0.00001	ns	ns	ns	ns

Post-test Sleep Latency

	Time (h) relative to drug ingestion							
Drug	-¼	¼	1¼	2¼	3¼	4¼	5¼	6¼
Melatonin	ns*	ns	0.04	0.0002	0.05	0.04	ns	0.008
Zaleplon	ns	ns	0.003	ns	ns	ns	0.02	ns
Zopiclone	ns	ns	0.0001	0.008	0.05	0.0002	ns	ns
Temazepam	ns	ns	ns	ns	ns	ns	ns	ns

*ns = not significant, or respective p-values.

(Table II). The interaction assessing the post-psychomotor impact of temazepam on sleep latency was not significant.

Drowsiness Data from 4-min Eyes-Closed Sessions

Like the EEG data, the subjective drowsiness data were collected before and after psychomotor testing (**Fig. 3**). We, therefore, added a pre/post factor to our ANOVA for this data set also, thus making a 3-way repeated-measures ANOVA with 5 levels of drug × 8 levels of trial × 2 levels of pre/post. This ANOVA yielded the following significant main effects: drugs, $F(4,88) = 17.93$, $p < 0.00001$; trials, $F(7,154) = 28.33$, $p < 0.00001$; pre/post, $F(1,22) = 114.06$, $p < 0.00001$; drug × trials, $F(28,616) = 4.87$, $p < 0.00001$; drug × pre/post, $F(4,88) = 4.64$, $p < 0.002$; trial × pre/post, $F(7,154) = 3.85$, $p < 0.0007$; and drug × trial × pre/post, $F(28,616) = 1.50$, $p < 0.05$. Post hoc testing of the main effect of pre/post indicated that the subjects experienced more drowsiness immediately after psychomotor testing ($p < 0.00001$) than immediately before psychomotor testing (3.39 s post-test vs. 2.50 s pretest). Post hoc testing of the main effect of drug revealed that zopiclone caused the largest impact on drowsiness (Fig. 3a and 3b).

Similar to our analysis of the EEG data, for the analysis of the drug effects on drowsiness we ran the 2 drugs × 8 trial ANOVAs in order to compare the effects of each drug against placebo. The drug × trial interaction to assess the impact of melatonin on pre-psychomotor test drowsiness was significant [$F(7,154) = 2.58$, $p < 0.02$]. Post hoc testing revealed that melatonin first caused an increase in pre-psychomotor test drowsiness within ¼ h post-ingestion ($p < 0.007$, **Table III**). This melatonin-induced drowsiness was still evident at the last psychomotor test 6¼ h post-ingestion ($p < 0.00008$). The corresponding drug × trial interaction to assess the impact of zaleplon on pretest drowsiness was significant [$F(7,154) = 2.36$, $p < 0.03$]. Post hoc testing

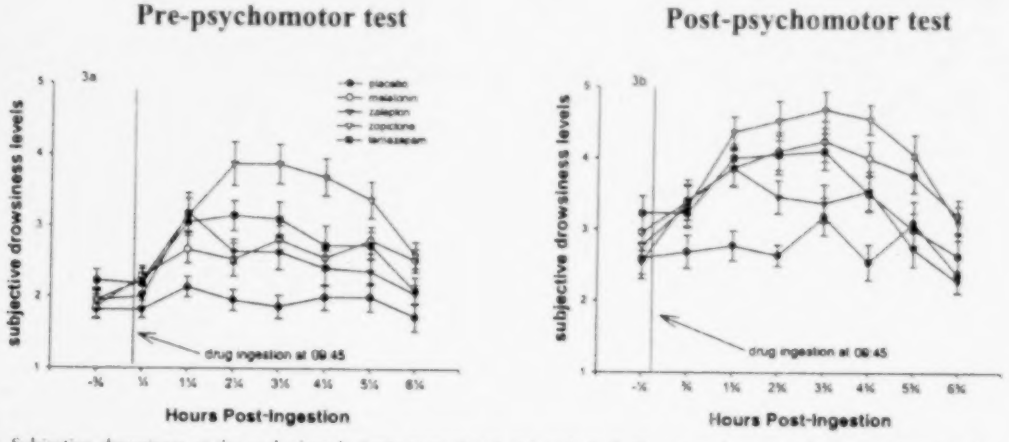

Fig. 3. Subjective drowsiness at the end of each 4-min eyes-closed rest periods, both pre- and post-psychomotor testing (Fig. 3a and 3b, respectively). All values are mean ± SEM and are plotted over drugs and hours post-ingestion.

TABLE III. POST HOC RESULTS FOR PRE- AND POST-PSYCHOMOTOR TASK, DROWSINESS DURING THE 4-MIN EYES-CLOSED PERIODS, WHERE EACH OF THE FOUR EXPERIMENTAL DRUGS IS COMPARED TO PLACEBO OVER EIGHT TRIALS.

Pretest Drowsiness

	Time (h) relative to drug ingestion							
Drug	−¼	¼	1¼	2¼	3¼	4¼	5¼	6¼
Melatonin	ns*	0.007	0.002	0.001	0.00001	0.002	0.00006	0.00008
Zaleplon	ns	ns	0.00001	0.001	0.0002	ns	ns	ns
Zopiclone	ns	ns	0.00006	0.00001	0.00001	0.00001	0.00002	0.00008
Temazepam	ns	ns	0.00003	0.00001	0.00001	0.0002	ns	ns

Post-test Drowsiness

	Time (h) relative to drug ingestion							
Drug	−¼	¾	1¾	2¾	3¾	4¾	5¾	6¾
Melatonin	ns	0.007	0.00004	0.00001	0.00006	0.00001	0.01	0.002
Zaleplon	ns	0.009	0.0001	0.003	ns	0.0004	ns	ns
Zopiclone	ns	0.023	0.00001	0.00001	0.00001	0.00001	0.0002	0.006
Temazepam	0.03	ns	0.0001	0.00004	0.007	0.002	ns	ns

*ns = not significant, or respective p-values.

revealed the first increase in zaleplon-induced drowsiness at 1¼ h after ingestion, with the effect peaking 2¼ h after ingestion, thereafter slowly subsiding to reach placebo levels by 4¼ h post-ingestion (Table III). The same interaction assessing the impact of zopiclone on pretest drowsiness was significant [$F(7,154) = 10.33$, $p < 0.000001$], with post hoc testing revealing the first significant zopiclone-induced increase in drowsiness 1¼ h after ingestion, the peak effect occurring over the next 3 h, and the effect still significant at the last psychomotor test session of the day 6¼ h after ingestion (Table III). The interaction evaluating the impact of temazepam on pre-psychomotor test drowsiness was significant [$F(7,154) = 4.26$, $p < 0.0003$]. Post hoc testing revealed that temazepam-induced drowsiness was first evident 1¼ h after ingestion with the peak effect occurring over the next 2 h, subsiding slightly at 4¼ h, and reaching placebo levels by 5¼ h after ingestion (Table III).

The drug × trial interaction evaluating the impact of melatonin on post- psychomotor test drowsiness was significant [$F(7,154) = 2.27$, $p < 0.03$]. Post hoc assessment confirmed the initial increase in melatonin-induced drowsiness occurred within ¾ h of ingestion, and remained high over the next 3 h before subsiding, but remained significant after the last psychomotor test session of the day 6¾ h after ingestion (Table III). The drug × trial interaction assessing the impact of zaleplon on post-psychomotor test drowsiness was significant [$F(7,154) = 4.12$, $p < 0.0004$]. Post hoc testing confirmed this zaleplon-induced increase in post-test drowsiness was first evident at ¾ h after ingestion, with peak effect occurring 1¾ h post-ingestion, and except for a loss of significance 3¾ h after ingestion (due to a transient increase in drowsiness while the subjects were on placebo), zaleplon-induced post-psychomotor test drowsiness remained significantly elevated until 4¾ h after ingestion (Table III). The interaction assessing post-test zopiclone-induced drowsiness was significant [$F(7,154) = 5.52$, $p < 0.00001$]. Post hoc testing first revealed an increased post-test zopiclone-induced drowsiness within ¾ h of ingestion, with the effect at peak levels over the subsequent 4 h, thereafter subsiding somewhat but still significant after the last psychomotor test session of the day 6¾ h after ingestion (Table III). The interaction assessing the post-test impact of temazepam on drowsiness was significant [$F(7,154) = 2.84$ $p < 0.008$]. Post hoc testing reveals an increase in drowsiness after the first psychomotor test session (i.e., before ingestion of temazepam). This was theorized to be a fatigue effect due to having just completed the baseline psychomotor test session. The first post-ingestion/post-psychomotor test increase in drowsiness due to temazepam is evident 1¾ h after ingestion with the effect peaking 2¾ h after ingestion, decreasing over the next 2 h, and reaching placebo levels by 5¾ h post-ingestion.

DISCUSSION

During the 4-min eyes-closed sessions, all drug conditions caused increases in total sleep, decreases in sleep latency, and increases in subjective drowsiness, either immediately before or immediately after psychomotor testing. The largest effects on total sleep, sleep latency, and drowsiness were attributable to zopiclone.

The pre- and post-psychomotor test differences in sleep latency, total sleep, and subjective drowsiness taken during the 4-min eyes-closed sessions and which are evident across all drug conditions, including placebo, indicate that the psychomotor test sessions were fatigue-inducing. Essentially, the post-psychomotor test increases in total sleep and corresponding decrease in sleep latency amount to a 'task effect' while the improvement in these parameters after the short rest period between adjacent psychomotor test sessions constitute a 'break effect.' This 'task effect' and 'break effect' have been previously documented in our laboratory (1,11).

Immediately before each psychomotor test session, melatonin did not result in any significant amounts of sleep (Fig. 1a) or changes in sleep latency (Fig. 2a).

However, melatonin did result in increased subjective drowsiness within 15 min of ingestion, which lasted throughout the entire 7-h post-ingestion period (Fig. 3), immediately before and immediately after each psychomotor test session, with drowsiness significantly more pronounced immediately after psychomotor testing (Fig. 3b) relative to before psychomotor testing (Fig. 3a). The 6-mg time-released formulation of pharmaceutical grade melatonin (Circadin®) produced significantly elevated plasma levels between 45 min and 6¾ h post-ingestion, but did not result in an impact on performance (9). We believe that because the time-released formulation of melatonin resulted in much lower blood levels than regular-release melatonin, it did not cause an impact on performance. Melatonin is not yet approved for use in Canada and regulatory approval must be obtained for its use in research. However, in jurisdictions where it is approved, it could be used in support of military operations as a mild, normally well-tolerated soporific which has been demonstrated to facilitate early circadian sleep in our laboratory (8), and during Canadian Forces Air Transport Operations in support of our troops in Bosnia (10).

Zaleplon produced a significant transient 1-h increase in total sleep and a corresponding 1-h reduction in sleep latency both before (Figs. 1a and 2a) and after psychomotor testing (Figs. 1b and 2b). Zaleplon also increased drowsiness for 3 h prior to psychomotor testing and for approximately 5 h post-psychomotor testing (Figs. 3a and 3b, respectively). The plasma levels of zaleplon were back to placebo level by 5 h post-ingestion (9). Zaleplon, in the dose we used, lived up to its reputation as a short-acting medication that causes transient performance impairment, has significant short-acting hypnotic power, and is quickly eliminated. Zaleplon would be a good choice of medication to facilitate sleep where the medicated individual might have to awaken from sleep no earlier than about 3 h after ingestion, and be expected to function with minimal impact on performance.

The zopiclone-induced increase in total sleep and corresponding reduction in sleep latency (before psychomotor testing, Figs. 1a and 2a, Tables I and II) were first evident 1¼ h post-ingestion and returned to placebo levels just before the last psychomotor test session at 6¼ h after ingestion. The post-psychomotor total sleep and sleep latency effects due to zopiclone were also first evident 1¼ h post-ingestion, but returned to placebo levels an hour earlier than the pre-psychomotor test values because a transient increase in those values attributable to placebo (due to task-induced fatigue) precluded significant zopiclone effects 5¼ h post-dose (Figs. 1b and 2b, Tables I and II). The subjective drowsiness levels attributable to zopiclone immediately prior to psychomotor testing were significant from 1¼ h post-ingestion through to just before the last psychomotor test session 6¼ h post-ingestion (Fig. 3a, Table III). The subjective drowsiness levels taken immediately after each psychomotor test session were significant earlier (¾ h post-ingestion) and remained significantly elevated until some time beyond 6¾ h post-ingestion (Fig. 3b, Table III). Zopiclone plasma levels were still very high 6¾ h after ingestion (9), suggesting that a longer interval, at least 8 h, is required after use before returning to operational duty. The effects of repeated daily administration were not assessed in this study, but clearly should be undertaken only with great caution.

The increase in total sleep and corresponding reduction in sleep latency attributable to temazepam immediately prior to psychomotor testing was evident only 2¼ h post-dosing, and was not evident at all after psychomotor testing largely because the post-testing increases in drowsiness on placebo precluded such an outcome (Fig. 1a and 2a, Tables I and II). Temazepam-induced drowsiness was evident between 1¼ h and 4¼ h post-dosing, both pre- and post-psychomotor testing. Temazepam is no longer used by the Canadian Forces, but could have benefits in other jurisdictions. However, care should be taken to ensure optimum dosage and optimum formulation (hard gelatin vs. soft gelatin capsule) in order to obtain the desired effects. Similar to zopiclone, in this study plasma temazepam levels were still elevated 7 h after ingestion. However, there is evidence that they are quite low 24 h post-ingestion (3). Nevertheless, repeated daily dosing for individuals who must sustain high psychomotor performance (such as military personnel) should only be considered after careful deliberation.

CONCLUSIONS

The time-released formulation of melatonin, while not a hypnotic, has been demonstrated in our earlier work (8,10) and in our current work to have enough soporific efficacy to facilitate early circadian sleep. Temazepam can be helpful as a hypnotic when its use is rationalized in terms of the appropriate dose and formulation to provide the correct pharmacokinetics to achieve the desired end result. Zaleplon is an effective mild and short-acting hypnotic producing moderate short-lasting impact on performance. Zopiclone is more sleep compelling and longer lasting than zaleplon and produces a very significant decrement in performance up to 7 h post-ingestion. The pre-psychomotor test sleep inducing power of the test medications in decreasing order of magnitude of effect were zopiclone, zaleplon, melatonin, and temazepam. The corresponding post-psychomotor effects in decreasing order were zopiclone, melatonin, zaleplon, and temazepam.

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